Applicants have amended the specification to refer to Table 2, much in the manner as a drawing would be referred to under a "Brief Description of the Drawings."

Applicants appreciate the Examiner calling their attention to the description of the properties of Analog #3 at page 38. However, this description is correct; LH and CG exhibit similar biological properties and bind to the same receptor.

As to the language "partial CTP unit or variant thereof," attention is called to the definition of "partial CTP" on page 12, beginning at line 18 and to the definition of "variant" beginning on page 13 at line 20. The partial CTP must contain at least one glycosylation site. Since this must be retained, similarity to CTP must be maintained as well.

The dependency of claim 4 has been corrected.

Priority

Although it does not appear to be an issue, it should be noted that disclosure of the linker unit as a Gly-Ser repeat or as having 1-16 amino acids, is described in U.S. Serial No. 08/199,382 filed 18 February 1994, as are the specific formulae recited in Table 1. Other features, indeed, are entitled to the priority of U.S. Serial No. 08/289,396 filed 12 August 1994.

As to joint ownership, all claims are directed to the same joint invention and were thus jointly owned at the time the invention was made. As discussed at the interview, the joint inventors at the time of filing of the applications relied on for benefit assigned their interests to different institutions. Application 08/199,382 filed 18 February 1994 is assigned of record to SensiTest. The remaining applications from which priority is claimed are assigned to Washington University. However, the application herein claims a single invention, as recognized by the Office. The invention is directed to recombinant materials and methods for production of single-chain forms of the glycoprotein hormones FSH, LH, CG and TSH. The presentation of dependent claims directed to specific embodiments of this invention does not remove these claims from the aegis of the joint invention contained in each. It is of no consequence whether, taken out of the context of the joint invention, such specific embodiments might themselves be patentable thereover. They are not out of the context of the joint invention. Accordingly, the claims herein are directed only to a single invention which at all times was assigned to the same assignee -- previously to both SensiTest and Washington University, and, by virtue of subsequent assignment from SensiTest, now to Washington University alone.

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The Art Rejections

All claims were rejected over the combination of Thomason with two documents by Reddy and, in certain instances, in further combination with additional tertiary references. In all cases, applicants believe that the rejection must fail as the hindsight combination of Thomason with the two Reddy documents is neither sufficient to defeat patentability of the broader claims, nor does it provide an adequate basis for combination with the tertiary references as applied to the narrower claims.

Thomason is cited for an asserted disclosure of a general proposition that multimeric proteins can be supplied in a single chain polypeptide form. However, a review of the disclosure of Thomason reveals that it pertains, in reality, only to PDGF and only even purports to pertain to multimeric proteins wherein the subunits are linked covalently through disulfide bonding. See column 3, lines 45-52. PDGF is indeed of this type. The claims granted in Thomason are correctly limited to proteins of the PDGF family. The "PDGF family" is defined as naturally occurring dimeric polypeptides having at least about 20% amino acid sequence homology to the PDGF homologous region and having a total of eight cysteine residues within the PDGF homologous region such that the cysteine residues are highly conserved (column 4, lines 57-62). The necessity for conservation of the cysteine residues testifies to the importance of the disulfide linkages.

Even among disulfide linked multimers, it is apparently recognized that single-chain forms of one type of protein do not render obvious single-chain forms of another. The limitation of the claim scope in Thomason to proteins of the PDGF family is clearly mandated in view of the prior disclosures of other disulfide-bonded multimers which have been prepared successfully in single-chain form. One of these is cited by applicants on page 2 of the specification, beginning at line 22. As there noted, a single-chain form of monellin, is described in U.S. Patent No. 5,264,558. The cited patent was granted on 23 November 1993 based on a series of applications which have an earliest priority date of 18 January 1990. Thus, the cited single-chain monellin document is clearly prior art under 35 USC 102(e) with respect to Thomason. Documents describing this single-chain form were also published in the intervening years and the description of single-chain monellin was thus documented in references available with respect to Thomason under 35 USC 102(b). These publications include PCT application

WO 88/10265, European applications 318,580 and 323,489 and an article by Kim, S.H., *et al.*, *Protein Engineering* (1989) 2:571-575. The Examiner in Thomason (and the Examiner here) apparently did not even consider these germane. This is logical since extrapolation from one type of protein to another in this context is not justified. As the claims in Thomason are limited to PDGF, it is reasonable to conclude that the monellin documents are not patent-defeating prior art as to Thomason, just as Thomason should not be considered patent-defeating prior art to the present claims.

Still another class of well known single-chain forms of cystine-linked dimers are the single-chain antibodies. The technology relating to single-chain antibodies was well enough established that phage display of such antibodies was disclosed in WO 88/06630, i.e., in 1988.

Thus, the general notion of preparing multimers that are natively coupled using disulfide links in a single-chain fusion protein form was well established in the art at the time of Thomason's application. The patentability of Thomason's single-chain form clearly resides in its applicability to PDGF *per se*.

Thus, it is apparent that the invention herein lies not in the generic concept of linking any multimer into a single-chain form, but in providing the single-chain form of the specific hormones claimed.

In addition, the glycoprotein hormones of the present invention in their native forms are heterodimers by *virtue of noncovalent interaction.* The mechanism whereby an appropriate conformation is assumed is thus entirely different from that of the Thomason dimers. Not only does the art not suggest providing the four glycoprotein hormones in single-chain form, there is no precedent of which applicants are aware for making a single-chain form of multimers where the multimers are associated through noncovalent interaction.

Thus, the combination of Thomason with the two Reddy documents does not on its face result in the invention even once the documents have been combined. The Thomason document relates only to disulfide-linked multimers; there is no bridging document to connect with the Reddy documents which describe FSH, i.e. connects disulfide bonded multimers to noncovalently bound multimers.

Applicants understand the point made by the Examiner at the interview that the art facing the present invention is cumulative -- i.e., that the application of the single-chain technology associated with monellin and single-chain antibodies to growth factors such as PDGF brings the

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state of the art closer to the single-chain glycoprotein hormones of the present invention. Leaving aside for the moment the highly relevant fact that all of the art pertains to disulfide-linked dimers or multimers and the present invention does not, applicants point out that this "cumulation" does not suggest application of the single-chain technology to the four glycoprotein hormones. The documents describing single-chain monellin, single-chain antibodies, and single-chain PDGF will be scanned in vain for any suggestion that the single-chain technology be applied to hormones of any kind, much less to the specific glycoprotein hormones that are the subject of the present invention. And, of course, the Reddy documents will be searched in vain for any suggestion that the hormones described in Reddy be prepared in single-chain form. Applicants are aware that an explicit suggestion of the invention need not be found in the art, but here there appears to be nothing other than the invention that would suggest the combination of the Reddy documents with Thomason.

As discussed at the interview, the notion that the ordinarily skilled practitioner of the art would be sitting in a room wall-papered with all of the prior art, all of which is fair subject for combination, has been disavowed by the courts. We will leave aside the common-sense recognition that this is clearly impossible when, as is the case for Thomason, the art is art only under 102(e) and thus could not possibly have adorned the walls of the practitioner. The wallpaper analogy arose in *In re Winslow*, 151 USPQ 48 (CCPA 1966) and the court distanced itself from this decision just five years later in *In re Antle*, 170 USPQ 285 (CCPA 1971). The opinion in *Antle* was written by Judge Rich, the same judge who wrote the *Winslow* opinion and who was clearly disturbed by the acceptance of the wallpaper analogy. As Judge Rich wrote in the *Antle* decision, this language "does not apply in cases where the very point in issue is whether one of ordinary skill in the art would have *selected* without the advantage of hindsight and knowledge of the applicants' disclosure the particular references which the Examiner applied." (Emphasis in the original) That is precisely the case here.

The opinion continues: "As we also said in *Winslow*, 'section 103 requires us to presume full knowledge by the inventor of the *prior* art *in the field of his endeavor*' but it does not require us to presume full knowledge by the inventor of prior art outside the field of his endeavor. It only requires us to presume that the inventor would have that ability to select and utilize knowledge from other arts reasonably pertinent to his particular problem which would be expected of a man of ordinary skill in the art to which the subject matter pertains." Here, the

applicants' field of endeavor is the glycoprotein hormones, and especially the three gonadotropins. Thomason is clearly outside the field, and does not address the problem to be solved. Thomason seeks to solve the problem of refolding. (See below) The problem that was sought to be solved in the present invention is multifaceted. As stated in the specification, at page 6, the single-chain forms have a number of advantages -- they are more stable, they can more easily be produced recombinantly, and, more important, they provide an alternate form thus permitting fine tuning of activity levels and of *in vivo* half-lives. They also provide unique starting materials for identifying truncated forms with the activity of the dimer.

The Federal Circuit in *Kimberly Clark v. Johnson & Johnson*, 223 USPQ 603 (Fed. Cir. 1984) went somewhat further and stated "We hereby declare the presumption that the inventor has knowledge of all material prior art to be dead." It is true that this statement was made in connection with a determination of whether there had been fraud on the Patent Office by virtue of failure to disclose documents; however, the court recited the public policy considerations -- that patentability should be denied only in order to prevent monopolization of what is in effect already in the public domain. Clearly, that cannot be the case here, where no suggestion is found in the prior art of providing single-chain forms of the glycoprotein hormones. As the Federal Circuit stated more recently in *Monarch Knitting Machinery v. Sulzer Morat GmbH*, 139 F3d 877 (Fed. Cir. 1998), "Defining the problem in terms of its solution reveals improper hindsight in the selection of prior art relevant to obviousness," citing *In re Antle*. Again, that appears to be what has been done here. The Office appears to have sought out art that disclosed the solution to the problems solved by applicants' invention, having been advised of the solution by the specification herein.

Thus, it is apparent, there is no suggestion in the documents themselves to make the combination. It has been recently reiterated by the Federal Circuit that there must be a stated rationale for combining documents. *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998). As the *Rouffet* court made clear, the Office must provide a reason to combine the documents other than using the invention as a guide. A closed list of three possible reasons was supplied by the court.

The first reason is that the documents themselves suggested the combination. Clearly that is not the case here -- there is nothing in Reddy that suggests that the FSH heterodimers have anything to do with PDGF or other multimeric proteins of Thomason; there is nothing in Thomason that refers to anything other than disulfide-linked multimers.

The second reason is in the nature of the problem to be solved. The Examiner cites "favorable renaturation kinetics and stability" as solutions to the problem of obtaining suitable conformation. While stability is one advantage of the single-chain proteins of the invention, this is not the problem that the present invention attempts to solve. As set forth on page 6 of the specification, the availability of the single-chain form provides additional flexibility in designing variants and muteins. It also provides ease of production. If one looks to Thomason as to the nature of the problem to be solved therein, one finds that the problem intended to be solved by Thomason is to provide analogs that are "more easily and rapidly refolded than unfused multimers" and "to eliminate the simultaneous formation of undesired polypeptide byproducts during refolding." (Column 2, lines 55 *et seq.*) These are not problems that the present invention is designed to solve. The production of the glycoprotein hormones according to the methods described in the specification results in the correct conformation initially. No refolding appears necessary. Thus, there is, in fact, no common problem to be solved.

The third basis cited by the court is plainly inapplicable here -- one of the references is so prominent that everyone would know it -- e.g., the Kohler-Milstein documents describing preparation of monoclonal antibodies.

Thus, it appears that the invention has been used as a guide to select the particular documents combined and made the basis for rejection. This is improper as has been repeatedly held by the court. For example, *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983); *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 316 (Fed. Cir. 1983).

Finally, even if the disclosure of Thomason, contrary to its terms, were considered to include reference to multimeric proteins which are not covalently coupled through disulfides, there would be no motivation to apply Thomason's approach to the particular species of heterodimers that is the subject of the present invention. The facts here are very similar to those in *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992). In *Jones*, a genus of salts of a particular herbicide, "dicamba," was disclosed in a prior art document. The particular salt claimed by Jones was within the genus of salts described, but not set forth specifically. The ammonium compound that formed the particular salt claimed in *Jones* was also known in the art. The court held that there was not even a *prima facie* case of obviousness with regard to this particular species, since there was nothing in the description of the genus that pointed to it, nor

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was there anything in the document describing the ammonium compound that suggested it be used as a counterion to form the salt with the acid that characterized the genus.

Here, at best, Thomason purports to disclose a genus of multimeric proteins that might be prepared in single-chain form. There is no suggestion in Thomason (and the Examiner kindly acknowledged this) that this technique be applied specifically to the four glycoprotein hormones made the subject of the present application. There is nothing in Thomason that points to that particular "species" if, indeed, it is included as a species, just as in Jones the prior art document made no suggestion that pointed to the claimed counterion. If anything, Thomason teaches away from any species which does not contain disulfide links between the subunits. Similarly, the Reddy documents make no suggestion that the FSH described therein be the subject of the modifications described in Thomason, just as there was no suggestion in the art that the ammonium compound in the secondary reference in *Jones* be the counterion to form the dicamba salt. There is nothing in *Jones* which indicates that the claimed ammonium salt of dicamba had any properties that were superior to those of any other salt. The failure of the primary reference to suggest focusing on the particular salt claimed by applicants and the fact that the ammonium ion that formed the salt was disclosed in another context led to the conclusion that there was no *prima facie* case. Here, there is no suggestion in either document for combination with the other.

Accordingly, there is no suggestion in the art even of the broadest claims -- claims 1, 11, 21 and 31. If the broadest claims are not suggested, neither can the dependent claims be suggested by this combination, even in further combination with additional documents.

Thus, as to the remaining rejections over these documents in combination with Zurawski *et al.*; or with Fares *et al.* or Boime, or in combination with Chaudhary, again, in these cases, there is no motivation to make the combinations with the tertiary reference absent the guidance of the invention. And there is no motivation to select the particular species claimed.

In view of the foregoing, it is believed that the considered claims, as well as those withdrawn from consideration, are patentable over the art.

Double Patenting

Finally, the Office requests a terminal disclaimer with respect to copending application 08/853,514 which claims the corresponding proteins. This application has been abandoned; a copy of the express abandonment is enclosed. Claims to the corresponding proteins will be

pursued in a divisional application based on the present one. The separation of these into two applications was a result of a restriction requirement in the original parent application 08/289,396, so no terminal disclaimer should be required. This, too was discussed at the interview, and a divisional will be filed presently.

Conclusion

There is no suggestion in the art to provide recombinant means to prepare single-chain forms of the four glycoprotein hormones included in the present application. Accordingly, it is believed that the present claims 1-39 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 295002005025. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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